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ISCHAEMIC HEART DISEASE

What should the role of bivalirudin be in the management of ACS? ► The REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events) trial showed that bivalirudin monotherapy, when compared with unfractionated heparin and glycoprotein (GP) IIb/IIIa inhibitors, led to similar rates of ischaemia and death in patients with stable or unstable angina undergoing percutaneous coronary intervention (PCI), but that rates of major and minor bleeding were significantly reduced. The ACUITY (Acute Catheterization and Urgent Intervention Strategy) trial was a prospective, randomised, multi-centre trial that compared a regimen of heparin and a glycoprotein IIb/IIIa inhibitor against bivalirudin plus a glycoprotein IIb/IIIa inhibitor or against bivalirudin alone in patients with moderate or high-risk acute coronary syndromes (ACS) undergoing an early invasive strategy. There were 13 819 patients with ACS randomised to one of these three antithrombotic regimens. The primary end points were a composite ischaemia end point (death, myocardial infarction or unplanned revascularisation for ischaemia), major bleeding, and the net clinical outcome (combination of composite ischaemia or major bleeding). Bivalirudin and a GP IIb/IIIa inhibitor, compared with heparin and a GP IIb/IIIa inhibitor, was associated with non-inferior 30-day rates of the composite ischaemia end point (7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%, respectively) and the net clinical outcome end point (11.8% and 11.7%, respectively). Bivalirudin alone, compared with heparin plus a GP IIb/IIIa inhibitor, was associated with a non-inferior rate of the composite ischemia end point (7.8% and 7.3%, respectively) and significantly reduced rates of major bleeding (3.0% *v* 5.7%, respectively; $p<0.001$) and the net clinical outcome end point (10.1% *v* 11.7%, respectively). Therefore, in this trial, when used alone, bivalirudin showed a slight non-significant increase in ischaemic events compared with heparin and GP IIb/IIIa used in conjunction, but the frequency of major bleeding events was significantly reduced, overall translating into a net clinical benefit for bivalirudin. What is its place? It seems reasonable to use bivalirudin in lower risk cases, but only if clopidogrel loading has been given.

▲ Stone GW, McLaurin BT, Cox DA, *et al*. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;**355**:2203–16.

In-stent restenosis can be treated with plaxitaxel ► The incidence of in-stent restenosis after percutaneous coronary intervention (PCI) ranges from 5% to 35% after the implantation of an uncoated stent. An even higher restenosis rate of 43% has been reported after treatment of a restenotic drug-eluting stent with a second drug-eluting stent.

In this study a novel balloon catheter coated with paclitaxel (3 μg/mm^2) was used to treat in-stent restenosis. Fifty-two patients were enrolled in a multi-centre, randomised, double-blind trial. The primary end point was late luminal loss as seen on angiography (at 6 months) with secondary end points including rates of restenosis and major adverse cardiac events (MACE). Quantitative coronary angiography revealed no significant differences in baseline measures between treatment groups. The mean ($\pm$SD) late luminal loss was 0.74 $\pm$ 0.86 mm in the group treated by conventional simple angioplasty compared with 0.03 $\pm$ 0.48 mm in those treated with the paclitaxel-covered balloon ($p=0.002$) at the 6-month follow-up. Forty-three per cent of patients in the uncoated-balloon group had restenosis compared with 5% in the paclitaxel-coated balloon cohort ($p=0.002$). The rate of MACE was significantly lower in the coated balloon (4%) group than in the uncoated group (31%) ($p=0.01$). This pilot study suggests that coronary in-stent restenosis can be successfully treated with a drug-coated balloon catheter. With current doubts about the long-term safety profile of drug-eluting stents, research into novel methods of preventing and treating in-stent restenosis remains an important priority.

▲ Scheller B, Hehrlein C, Bocksch W, *et al*. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N Engl J Med* 2006;**355**:2113–24.

The GRACE Risk Calculator—better than TIMI? ► Using data from 43 810 patients across four continents enrolled in the GRACE (Global Registry of Acute Coronary Events) registry, Fox and colleagues identified nine factors that independently predicted death, and the combined end point of death or myocardial infarction, in the period from admission to 6 months after discharge. The nine factors were age, heart failure, peripheral vascular disease, systolic blood pressure, Killip class, initial serum creatinine concentration, elevated initial cardiac markers, cardiac arrest on admission, and ST segment deviation. These factors were validated using the GUSTO (Global Utilization of Strategies for Total Occlusion) IIb dataset and a simple nomogram developed, which is available to physicians online (http://www.outcomes.org/grace). While thrombolysis in myocardial infarction (TIMI) scoring remains useful in patients eligible for reperfusion therapy, it is less useful in more general patients. Proof that selecting patients for treatment based on this risk score affects outcome is awaited. The GRACE tool is applicable to patients across the complete spectrum of acute coronary syndromes.

▲ Fox KA, Dabbous OH, Goldberg RJ, *et al*. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 2006;**333**:1091.

GENERAL CARDIOLOGY

What are the effects of statin therapy in patients with CHF? ► Go and colleagues identified 24 598 adults with a diagnosis of chronic heart failure (CHF) but no prior statin use and followed them for a median period of 2.4 years. The main outcome measures studied were death and hospitalisation for heart failure. Those starting statin therapy (51.4%) were more likely to be younger, male and have known cardiovascular disease, diabetes and hypertension. Incident statin use was associated with lower risks of death (adjusted hazard ratio (HR) 0.76) and hospitalisation for heart failure (adjusted HR 0.79) even after adjustment for other potential confounders. Incident statin use was associated with lower adjusted risks of adverse outcomes whether or not patients had known coronary artery disease. The benefit of statins in this setting could be attributable to the cholesterol-lowering effects, an improvement in vascular endothelial function, or the pleiotropic effects of statins. A prospective clinical trial to look at the effects of statins on the natural history of CHF in non-ischaemic cardiomyopathy would be worthwhile.

▲ Go AS, Lee WY, Yang J, *et al*. Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006;**296**:2105–11.

What is the impact of heart failure in the community? ► Most studies are hospital based and retrospective, and diastolic function is seldom systematically assessed based on standardised techniques. Bursi and colleagues recruited 556 patients at the time of diagnosis of heart failure. Echocardiography performed at this initial stage showed a preserved ejection fraction (EF; EF>50%) in 308 (55%) patients and was associated with older age, female sex and no history of myocardial infarction ($p<0.001$). Isolated diastolic dysfunction (diastolic dysfunction with preserved EF) was present in 242 (44%) patients. For patients with reduced EF, the presence of moderate or severe diastolic dysfunction was more common than when EF was preserved (odds ratio (OR) 1.67). Both low EF and diastolic dysfunction were independently related to higher levels of B-type natriuretic peptide. At 6 months, mortality was 16% for both

preserved and reduced EF groups. Thus in this community study, more than half the patients presenting with heart failure had preserved EF, with diastolic dysfunction being present in more than 40% of cases. Moreover, even when EF is preserved, mortality rates in patients with diastolic dysfunction remain high and comparable with those of patients with reduced EF. Systolic and diastolic dysfunction can often go hand in hand.

▲ Bursi F, Weston SA, Redfield MM, *et al*. Systolic and diastolic heart failure in the community. *JAMA* 2006;**296**:2209–16.

Does systolic blood pressure on admission give an indication of mortality risk in patients admitted with heart failure? ► Data from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry were used to examine the outcomes of 48 612 patients admitted with heart failure between March 2003 and December 2004. Of these, 41 267 had assessment made of left ventricular function, of which 21 149 (51%) had preserved left ventricular function. Patients were divided into quartiles by systolic blood pressure (SBP) at hospital admission (<120, 120–139, 140–161 and >161 mm Hg). Post-discharge outcomes were based on a prespecified subgroup of 5791 patients, who were assessed between 60 to 90 days. In-hospital and post-discharge mortality were selected as the main outcome measures. Fifty per cent of all patients had a SBP of higher than 140 mm Hg at admission; those with the higher SBPs were more likely to be female and black and to have preserved systolic function. In-hospital mortality rates decreased as SBP increased: 7.2% (<120 mm Hg), 3.6% (120–139 mm Hg), 2.5% (140–161 mm Hg) and 1.7% (>161 mm Hg) ($p<0.001$ for overall difference). Post-discharge mortality rates in the follow-up cohort by SBP at admission were 14.0%, 8.4%, 6.0% and 5.4%, respectively ($p<0.001$ for overall difference). This study showed that patients with a low SBP (<120 mm Hg) at hospital admission have a poor prognosis despite medical therapy, but it also identified that many patients hospitalised for heart failure in fact present with systolic hypertension.

▲ Gheorghiade M, Abraham WT, Albert NM, *et al*. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;**296**:2217–26.

Non-adherence to medications is common, but how serious a problem is this? ► Using data from the PREMIER registry (Prospective Registry Evaluating Myocardial Infarction: Event and Recovery Study), Ho and colleagues looked at the outcomes of 1521 patients who were all initially discharged on aspirin, β blockers and statins. At 1 month follow up, 184 patients had stopped using all three medications, 56 had stopped using two and 272 had stopped one; 1009 continued taking all three. Increasing age had an effect on discontinuation of medication therapy that was more pronounced in females (odds ratio (OR) 1.77) than males (OR 1.23). Patients who discontinued use of all medications at 1 month had lower 1-year survival (88.5% *v* 97.7%; $p<.001$) than patients who continued to take one or more medications. In a multivariable survival analysis, medication therapy discontinuation was independently associated with higher mortality (hazards ratio 3.81). These results were consistent when evaluating discontinuation of the use of aspirin, β blockers and statins separately. This alarming study reveals that medication discontinuation after myocardial infarction is common and can occur at an early stage after discharge. The authors suggest that the transition between hospital and outpatient care needs to be improved. This may be even more relevant in the era of drug-eluting stents, when discontinuation of anti-platelet medication may be rapidly disastrous

▲ Ho PM, Spertus JA, Masoudi FA, *et al*. Impact of medication therapy discontinuation on mortality after myocardial infarction. *Arch Intern Med* 2006;**166**(17):1842–7.

LVAD in heart failure ► The use of a left ventricular assist device (LVAD) to offload the myocardium in patients with acute severe heart failure has been reported to lead to myocardial recovery in small numbers of cases for a variable time period. Fifteen patients with severe heart failure of non-ischaemic origin were treated with a combination of LVAD and lisinopril, carvedilol, spironolactone and losartan to enhance reverse remodelling. All cases had been demonstrated to have markedly decreased cardiac output and required inotropic support. Once regression of left ventricular enlargement had been demonstrated, the β-2 adrenergic agonist clenbuterol was given to prevent myocardial atrophy.

Eleven patients recovered sufficient myocardial function to undergo explantation of the LVAD at a mean (±SD) of 320 ± 186 days. One patient died of intractable arrhythmias 24 hours after explantation; the only other death was at 27 months after explantation and was caused by carcinoma of the lung. The cumulative rate of freedom from recurrent heart failure was 100% at 1 year and 88.9% at 4 years' post-explantation, and the quality of life as assessed by the Minnesota Living with Heart Failure Questionnaire score at three 3 years was nearly normal. Fifty-nine months after explantation, the mean left ventricular ejection fraction was 64 ± 12%. This combined regimen of mechanical and pharmacological therapy may improve the frequency and sustainability of myocardial recovery in severe heart failure of non-ischaemic origin. Further studies will be necessary to demonstrate both the reproducibility and durability of these findings.

▲ Birks EJ, Tansley PD, Hardy J, *et al*. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med* 2006;**355**:1873–84.

BASIC SCIENCE

Aortic stenosis is like atherosclerosis ► It is known that aortic stenosis and coronary disease share risk factors. What about the mechanism? Normally cardiac valves are avascular, but in pathological states such as aortic stenosis the valve may start to express angiogenic factors causing neovascularisation and promoting the development of stenosis. Yoshioka *et al* studied the role of chondromodulin-1, an anti-angiogenic factor isolated from cartilage that is abundantly expressed in cardiac valves. They hypothesised that lack of chondromodulin-1 may lead to increased rates of stenosis. Deficiency of chondromodulin-1 resulted in an age-dependent increase in angiogenesis in mice, which was associated with valve pathology including calcification, valve thickening and turbulent blood flow. The pathological process was very similar to that which occurs in the elderly human population with aortic sclerosis. The group further demonstrated that in a mouse model (*Apoe* $^{-/-}$) chondromodulin-1 was absent in calcified regions of valves and this was associated with an increased density in the tissue microvasculature. Thus a relationship has been demonstrated for the first time between the lack of an angiogenesis inhibitor and valvular heart disease. There are likely to be other molecules involved in this process and further studies will be necessary in order to understand how these inhibitors function.

▲ Yoshioka M, Yuasa S, Matsumura K, *et al*. Chondromodulin-I maintains cardiac valvular function by preventing angiogenesis. *Nat Med* 2006;**12**:1151–9.

▲ Kalluri R, Zeisberg E. Controlling angiogenesis in heart valves. *Nat Med* 2006;**12**:1118–9.

Journals scanned

American Journal of Medicine; American Journal of Physiology: Heart and Circulatory Physiology; Annals of Emergency Medicine; Annals of Thoracic Surgery; Archives of Internal Medicine; BMJ; Chest; European Journal of Cardiothoracic Surgery; Lancet; JAMA; Journal of Clinical Investigation; Journal of Diabetes and its Complications; Journal of Immunology; Journal of Thoracic and Cardiovascular Surgery; Nature Medicine; New England Journal of Medicine; Pharmacoeconomics; Thorax

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